New Approaches to Genital Herpes Treatment and Prevention

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STD Advances Update

Honolulu, HI

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Overview

- Epidemiology and natural history
- Clinical impact
- Detection
- Treatment and prevention

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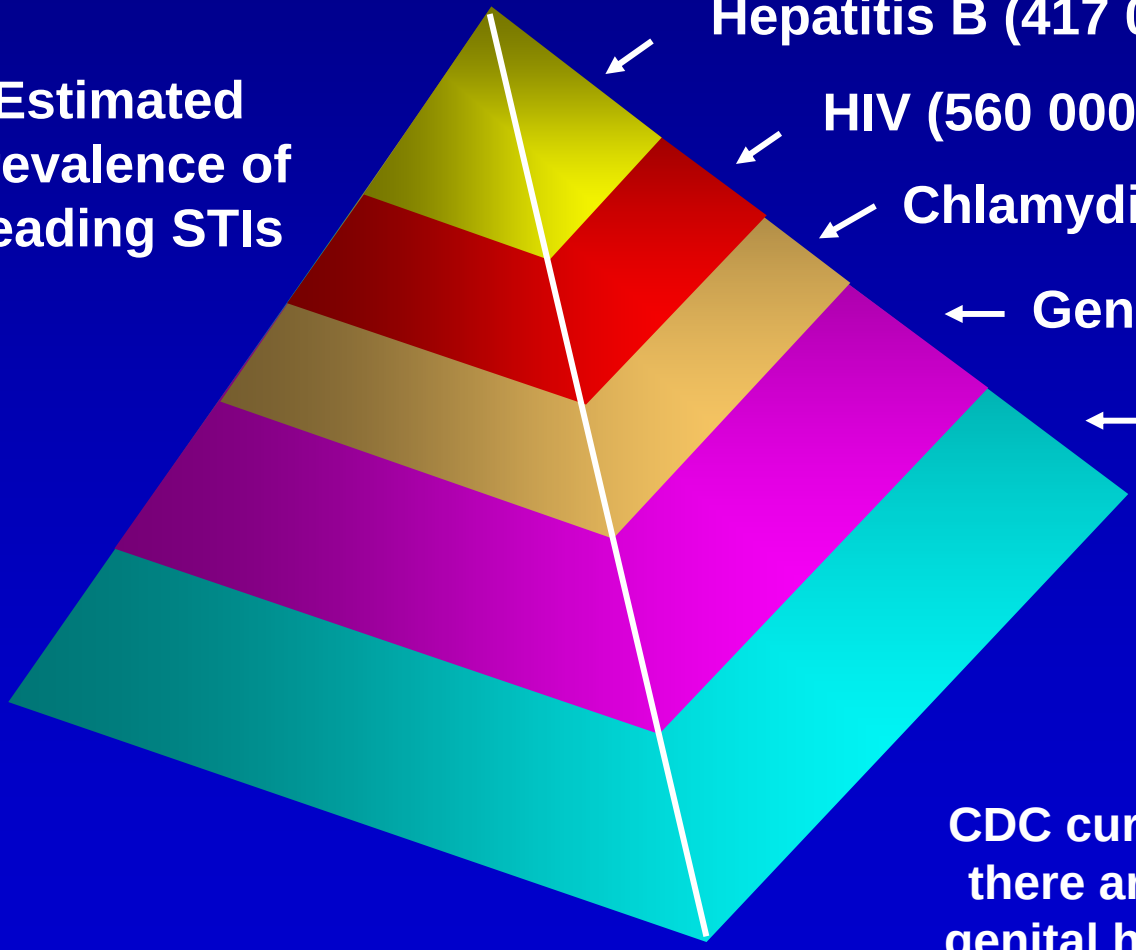
Herpes: the Most Prevalent STI in the USA

Estimated Prevalence of Leading STIs



Hepatitis B (417 000)

HIV (560 000)

Chlamydia (2 million)

← Genital HPV (20 million)

← Herpes (~50 million)

CDC currently estimates there are 1 million new genital herpes infections per year

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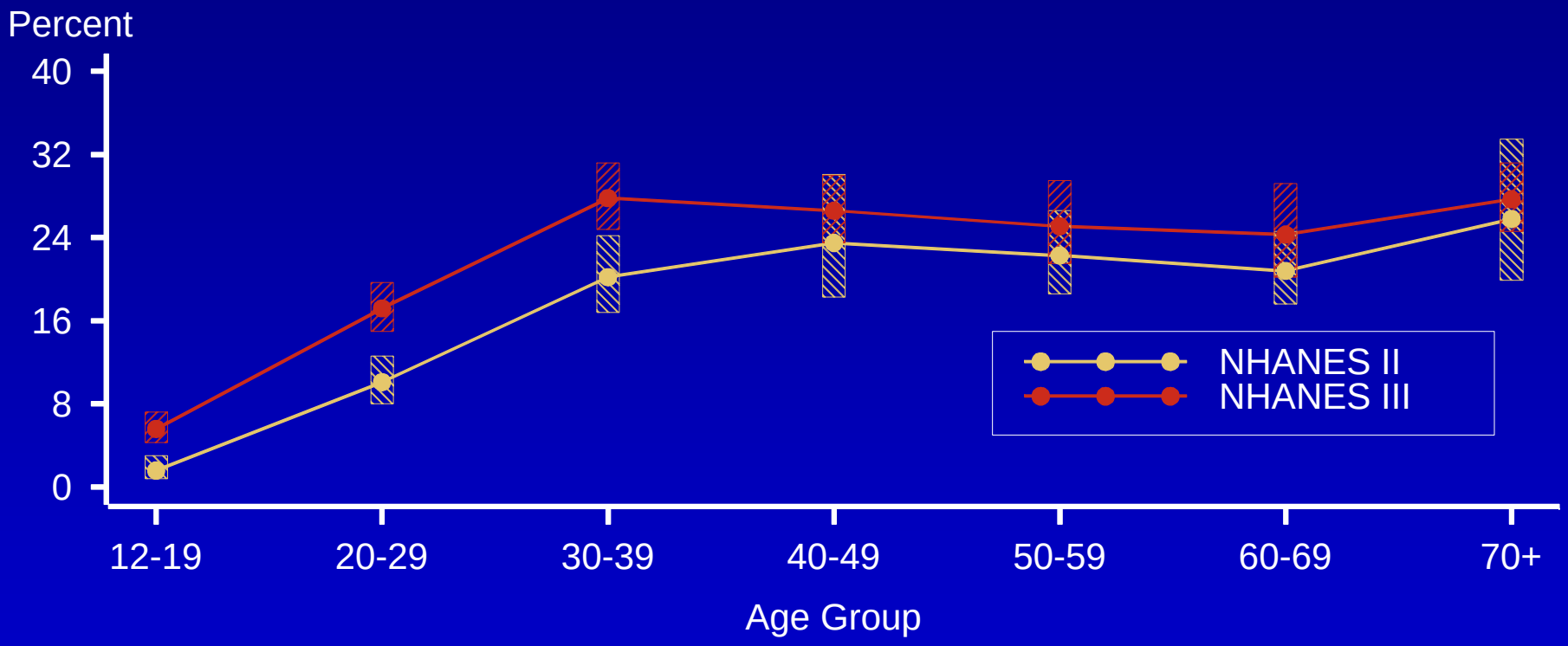
Herpes Simplex Virus

- HSV-1
  - ~50% infected by adulthood
  - Mostly orolabial (cold sores, fever blisters)
  - An increasing proportion of cases of primary genital herpes are caused by HSV-1 (15-30%)
- HSV-2
  - ~20% US population infected
  - Almost entirely genital; oral infection rare
  - Accounts for >95% of recurrent genital herpes

Seroprevalence of HSV-2

NHANES* II (1976–1980) and NHANES III (1988–1994)



Note: Bars indicate 95% confidence intervals.
*National Health and Nutrition Examination Survey

Fleming DT, et al. N Engl J Med. 1997;337:1105-1111

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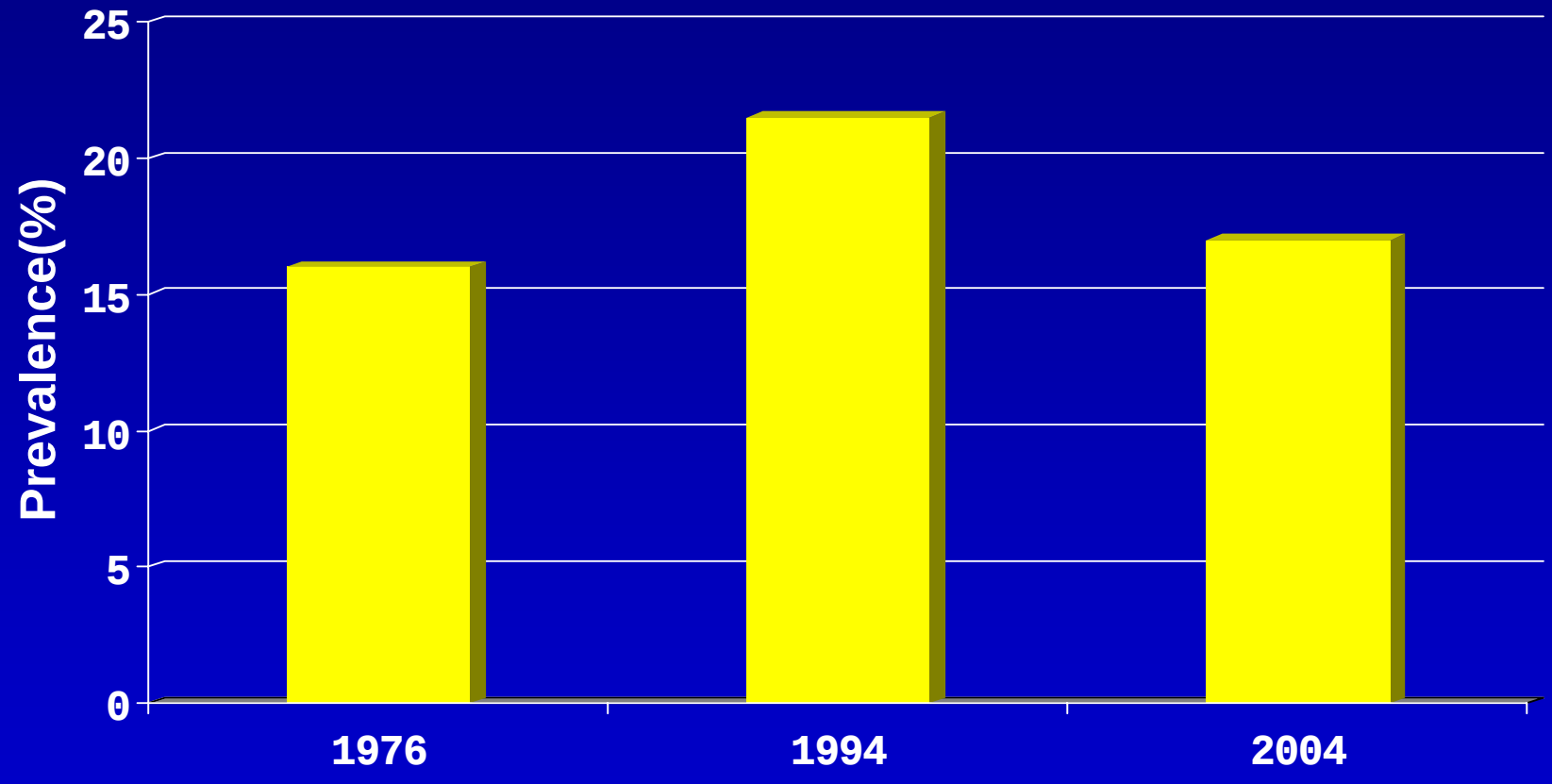
Trends in Herpes Simplex Virus 2 Age-Adjusted Seroprevalence in U.S. Adults Ages 14 - 49



Fleming DT, et al. N Engl J Med. 1997;337:1105-1111.

Xu F, et al. JAMA. 2006;396:964-973

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Risk Factors for HSV-2 Infection

- Independent predictors* for HSV-2 were:
  - Lifetime number of sex partners
  - Female gender
  - African American or Mexican American ethnicity
  - Older age

*OR >3 for each

Fleming DT, et al. N Engl J Med. 1997;337:1105-1111

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Prevalence of HSV-2 in Selected Populations

STD clinic attendees (male)	32%
STD clinic attendees (female)	52%
Primary care patients, Seattle	23%
University students, NC	4%
Women aged 18-29 in N.CA	34%
MSM in San Francisco	27%
HIV+ MSM in Baltimore	80%

Gottleib 2002, Wald 1997, Gibson 1997, Buchacz 2000, Turner 2000,Hook 1992

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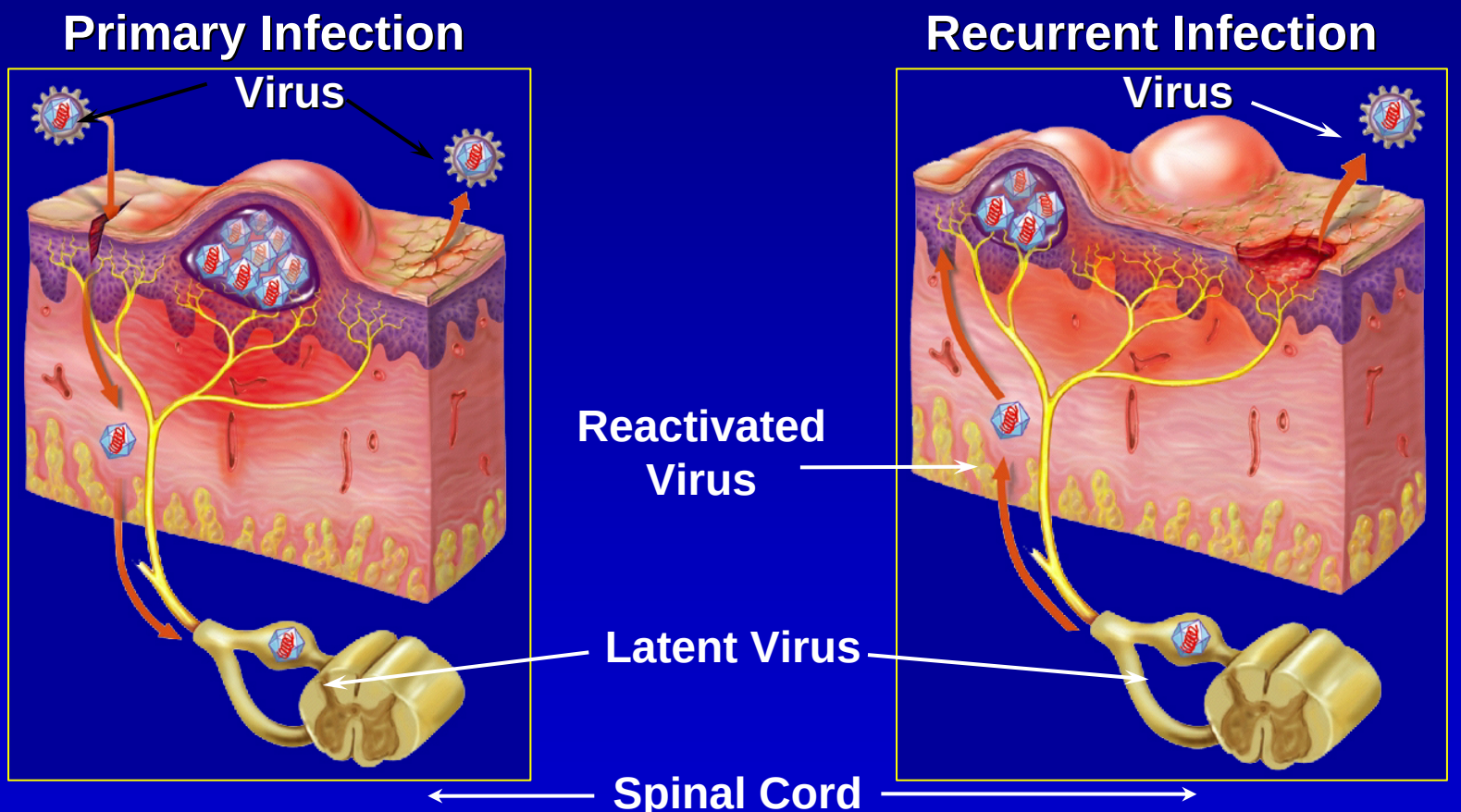
Natural History HSV-2 in Adults

- Primary infection: virus enters through skin or mucous membranes then establishes latency in spinal cord (S 2-4)
- Viral reactivations (recurrences): virus travels down axons causing lesions or asymptomatic shedding in genital area
- All infected persons have episodes of asymptomatic viral shedding

Pathogenesis



Clinical Impact

Genital Herpes Classifications

- First clinical episodes
  - **Primary**: first infection ever with either HSV type
  - **Non-primary**: newly acquired infection with HSV-1 or HSV-2 in a person seropositive to the other virus
- Recurrent episodes
  - Antibody is present to the same viral serotype when symptoms appear
  - Patient may not be aware of previous episodes
- Asymptomatic infection

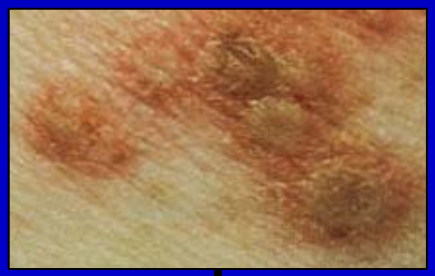
Baker DA and the ACOG Committee in Practice Bulletins—Obstetrics.
Int J Gynecol Obstet. 2000;68;165-174.

Classic Progression of Herpes Lesions

Prodrome

Early Redness/Swelling

Thin-Walled Fluid-Filled Vesicles and Pustules



Early Healing of Vesicles, Erosions, or Ulcers

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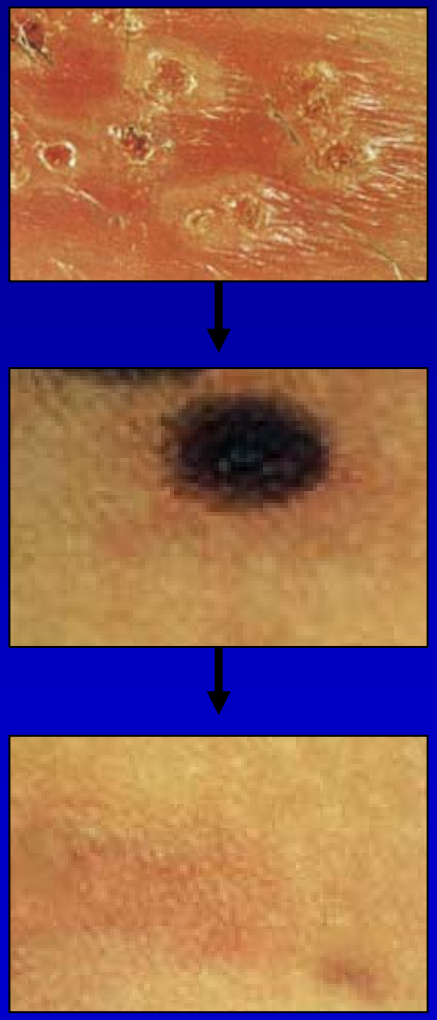
Progression of Herpes Lesions



Crusting

Scabbing

Healed Skin

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Primary Genital Herpes

- Incubation period ~ 4 days (2-14 day range)
- Systemic symptoms in up to 80% (fever, headache, malaise, myalgia)
- Local symptoms: pain, itching, dysuria, discharge, inguinal adenopathy
- Multiple painful lesions develop bilaterally
- New lesions may appear for up to 10 days, with mean duration of lesions 18 days
- Complications are not uncommon: aseptic meningitis (30%), autonomic dysfunction, dissemination

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Primary Herpes Penile Lesions

DOIA *Website, 2000*

Primary Herpes Vulvar Lesions

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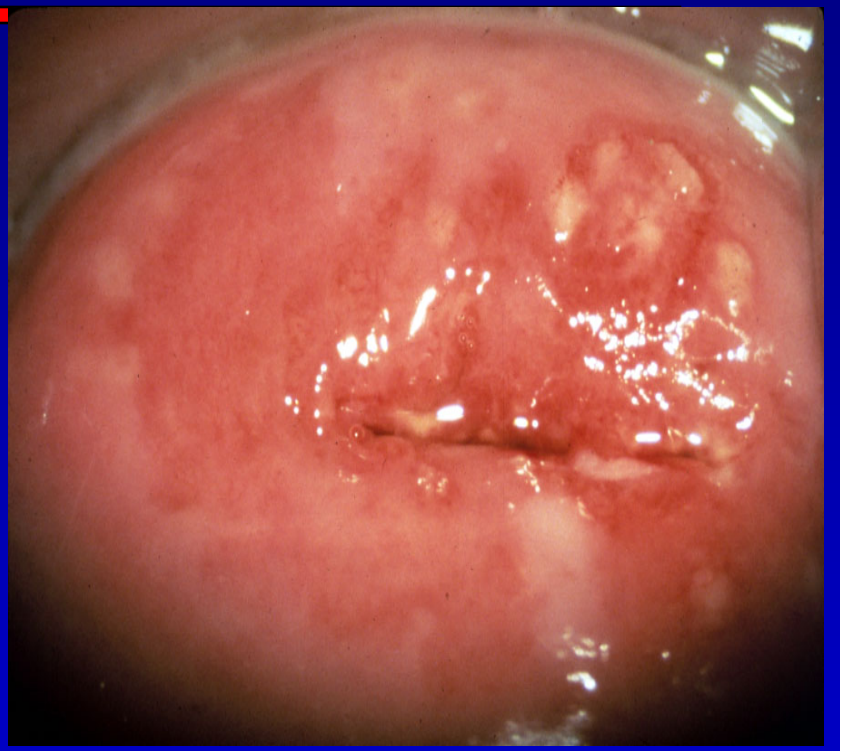
Herpes Cervicitis



Mosby *STD Atlas, 1997*

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Complications of Genital Herpes

- CNS Involvement
  - Aseptic meningitis
  - Transverse myelitis
  - Urinary retention
  - Constipation (more common with HSV proctitis)
- Extragenital Lesions
- Disseminated Infection
  - Meningitis, hepatitis, arthritis, pneumonitis
  - Pregnancy and eczema may predispose
- Neonatal Herpes
- HIV

Recurrent Genital Herpes

- Milder clinical illness
  - Less extensive distribution of lesions, typically unilateral,
  - Shorter duration of symptoms (5-10 days)
- Systemic symptom rare
- Prodrome common
- Complications rare
- Frequency variable
- May present as first clinical episode

Genital HSV-2 With More Frequent Outbreaks

- Patients with primary genital HSV-1
  - Recurrence rate:1.3 per year in first year and 0.7 second year
  - 43% of patients had no recurrence in first year and 67% no recurrence in second year
- Patients with primary genital HSV-2
  - Recurrence rate: 4.1 per year in first year
  - 38% with at least 6 recurrences and 20% with more than 10 recurrences in first year.

Engleberg,STD 2003. Benedetti, Annals, 1994

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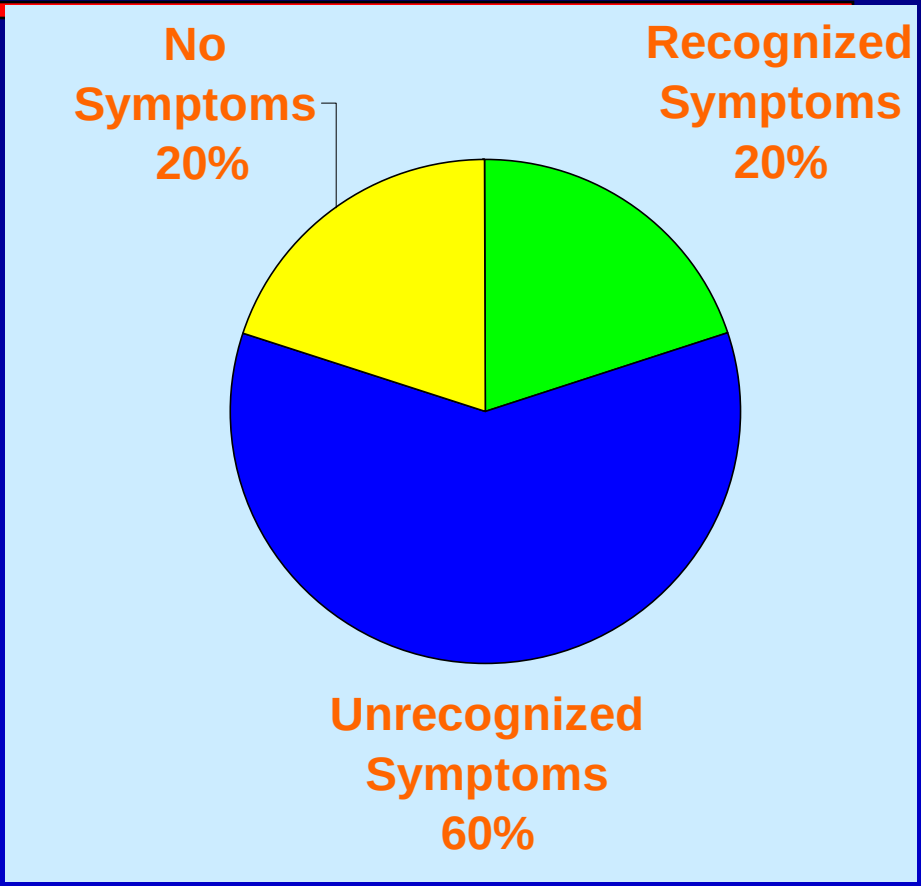
Subclinical/Asymptomatic Herpes

- Only 20% of people seropositive for HSV-2 recognize their infection
- 60% have unrecognized or atypical infections
- 20% have no symptoms



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What Men Say They Think They Have

- Folliculitis
- Jock itch
- “Normal” itch
- Zipper burn
- Hemorrhoids
- Allergy to condoms
- Prostatitis
- Irritation from
  - Tight jeans
  - Sexual intercourse
  - Bike seat
- Insect or spider bites

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Atypical Herpes Sores

SFCC

What Women Say They Think They Have

- Yeast infection
- Vaginitis
- Urinary tract infection
- Menstrual complaint
- Hemorrhoids
- Heat rash
- Postcoital soreness
- An ingrown hair
- Allergy to
  - Condoms
  - Sperm
  - Spermicide
  - Elastic/pantyhose
- Irritation from
  - Bike seat
  - Shaving
  - Douching

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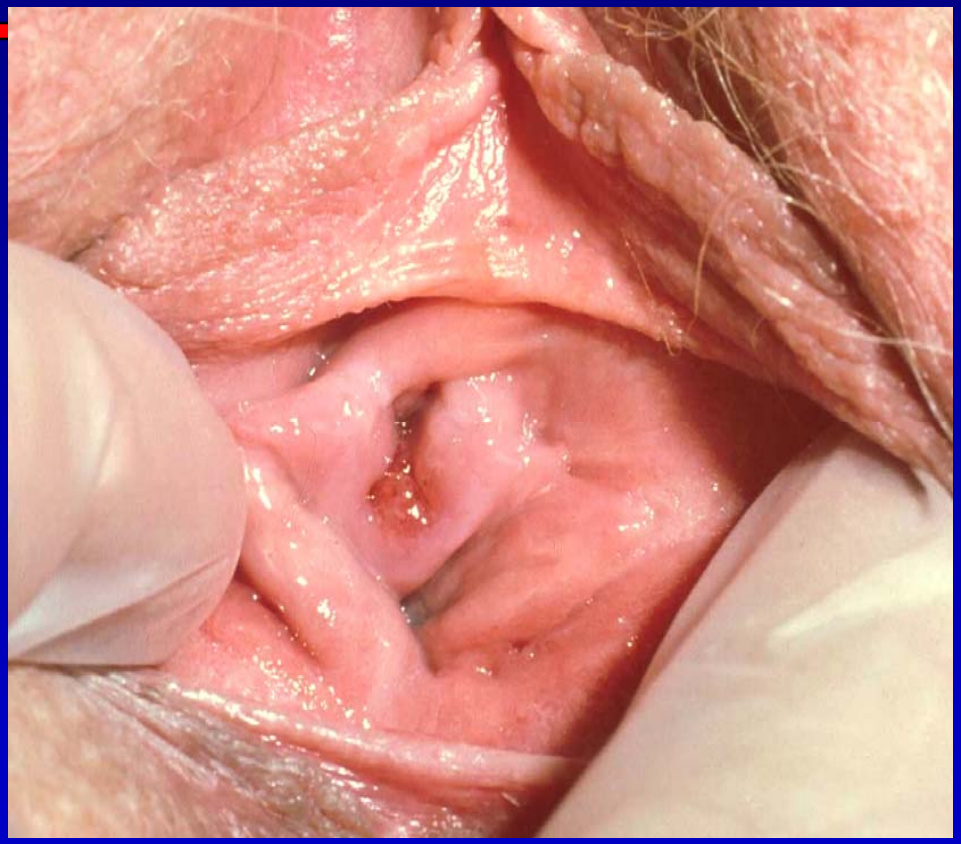
Atypical Herpes Sores in Women



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Atypical Herpes Sores in Women

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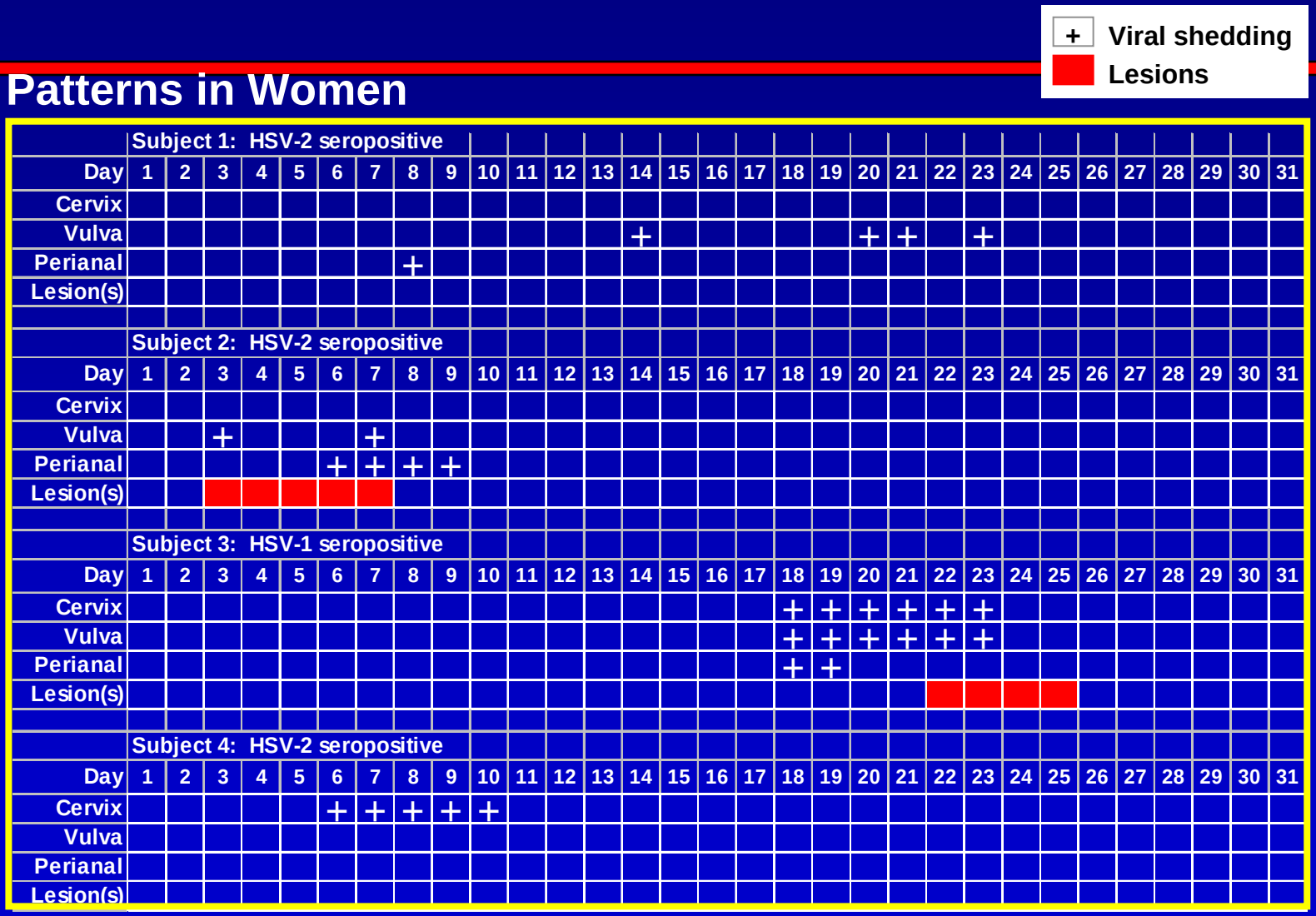
Asymptomatic Viral Shedding

- The majority (>90%) of people with genital HSV-2 shed virus asymptomatically
- Genital herpes is frequently transmitted during periods of asymptomatic shedding
- Frequency of asymptomatic shedding is highest in first year after acquisition
- Uncommon in HSV-1 genital infection

Viral Shedding May Occur in the Absence of Lesions



Wald A et al. *N Engl J Med*. 1995;333:770-775.

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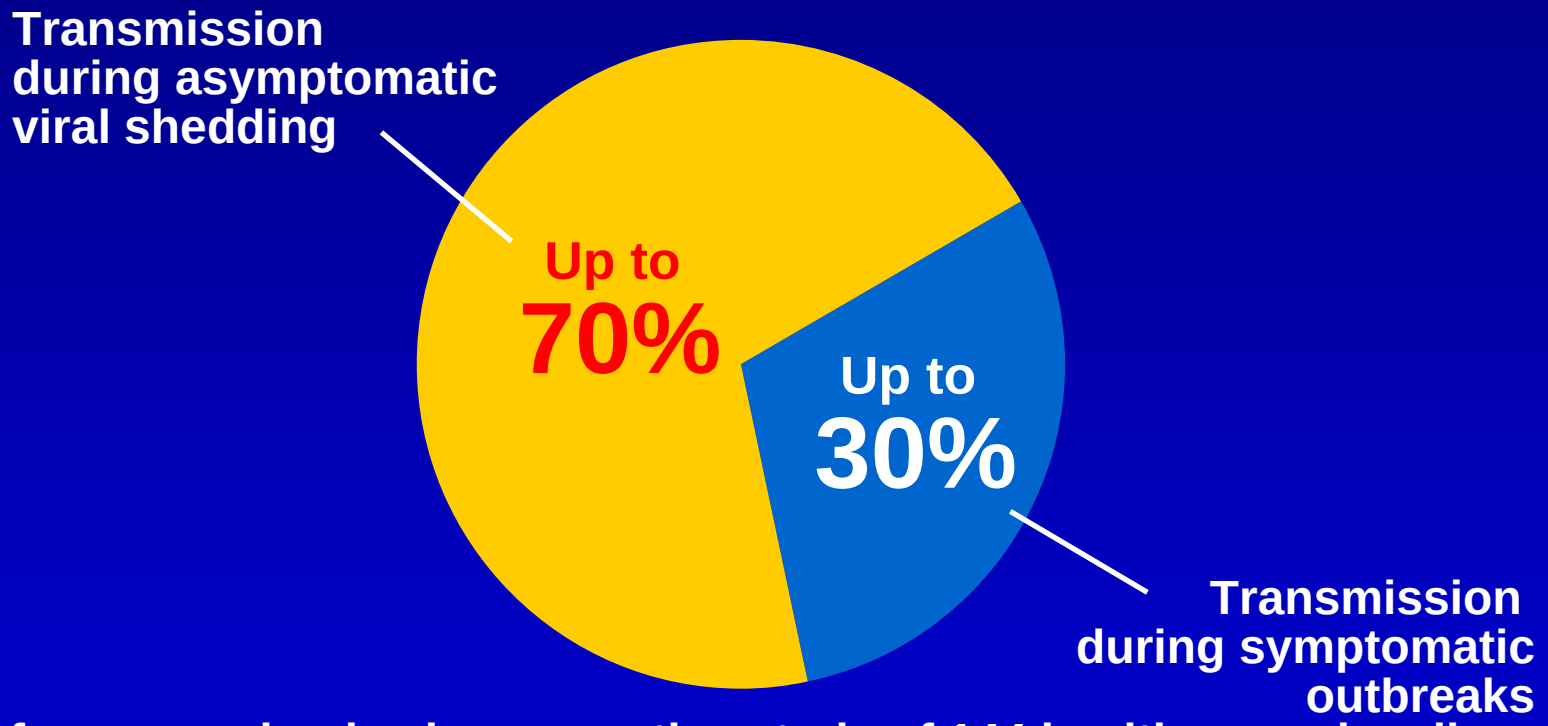
Up to 70% of Transmission May Occur During Asymptomatic Viral Shedding



Results from a randomized, prospective study of 144 healthy couples discordant for genital herpes. Couples were followed for a median of 334 days, during which time 9.7% of partners became infected with genital herpes.
Only 15% used condoms routinely despite counseling.

Adapted from Mertz GJ et al. *Ann Intern Med*. 1992;116:197-202.

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Neonatal Herpes

- Neonatal infection occurs in 1/3,000 -

1/ 20,000 births in US (1/8,700 in CA)

- Clinical disease manifests at 3-30 days of age
  - Skin, eye or mucous membrane (SEM): 45% (no mortality associated)
  - CNS: 35% (15% mortality, 65% serious sequelae
  - Disseminated: 25% (50% mortality)
- Half of cases caused by HSV-2 (55%)

NIAID Collaborative Antiviral Study Group; Brown NEJM 2002

Neonatal Herpes Skin Infection

Mosby *STD Atlas, 1997*

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Herpes: Transmission Rates by Stage of Maternal Infection

- Primary (acquired during 3rd trimester): up to 50%
- Recurrent symptomatic (at time of delivery): 4%
- Recurrent asymptomatic (at delivery): < 0.04%

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Interaction of HSV and HIV

- Observational studies show HSV-2 seropositive have ~ 2-3 times risk of acquiring HIV-1
- HSV-2 has been shown to raise genital levels of HIV-1
- A recent randomized trial has shown suppressive treatment of HSV reduces genital and plasma levels of HIV-1 (Nagot et al. NEJM. 2007;356(8):790-9)
- Studies now ongoing will assess whether suppressive therapy reduces risk of HIV acquisition or reduces HIV transmission in HIV-1 discordant couples

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Detection

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HSV Diagnosis

- Clinical diagnosis should be confirmed by lab testing:
  - FIRST LINE: Direct virologic tests of lesion (culture, DFA, EIA, PCR)
  - SECOND LINE: Type-specific serologic tests

Direct Virologic Tests

Culture

- Highly specific; sensitivity depends on stage of lesions and proper collection technique
- Viral typing can be done on positive specimens

DFA/ELISA

- Equal sensitivity to culture; less specific
- Only DFA can differentiate HSV-1 and HSV-2

PCR

- Highly sensitive and specific for diagnosis in clinical specimens. Only FDA approved for CSF. Available from some reference labs with internal verification.

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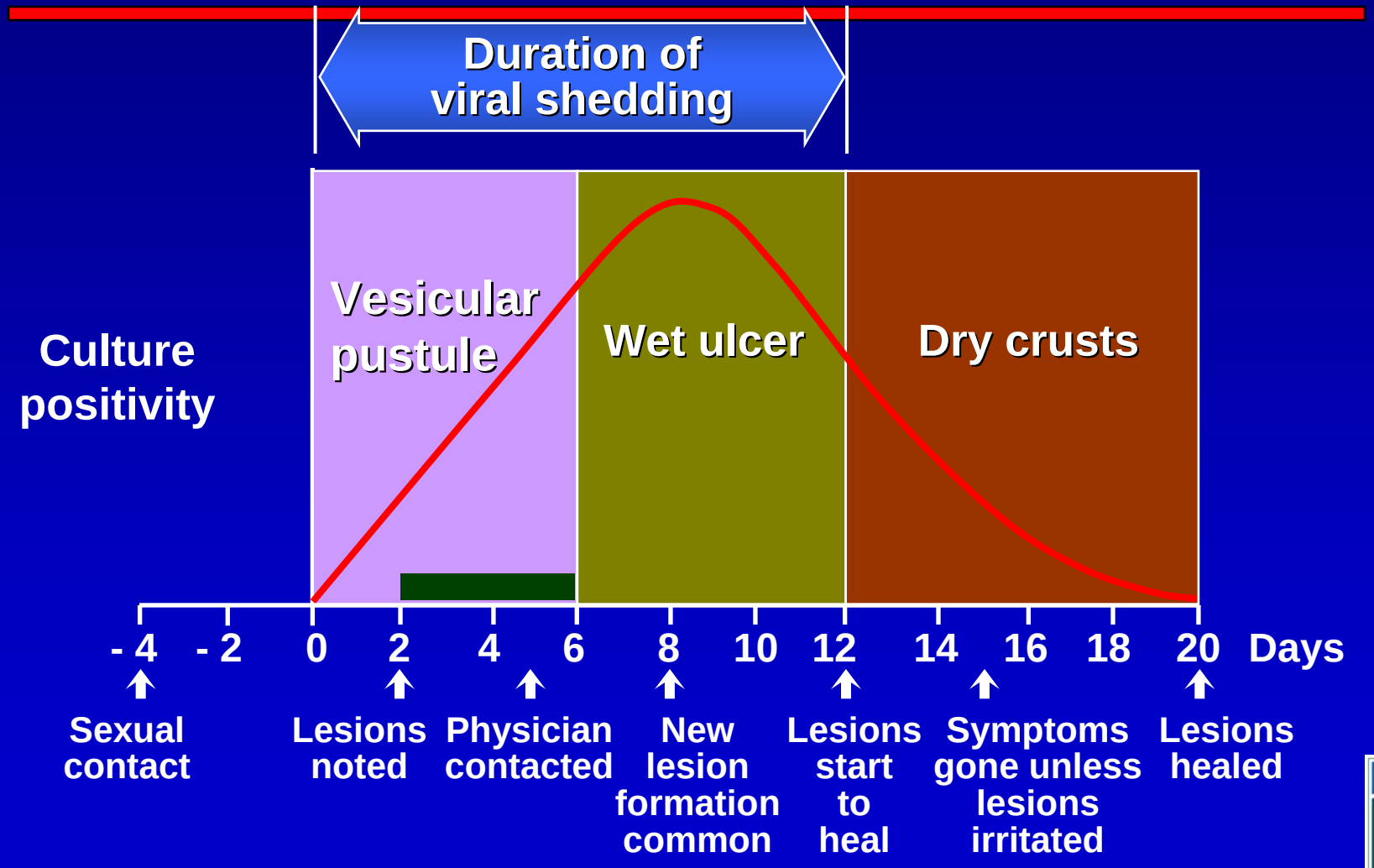
Culture Positivity Correlates with Age of Lesion



Adapted from Corey L, et al. *Sexually Transmitted Diseases.* 1999:285-312.

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Type-Specific HSV Serology Tests

- Focus Technologies
  - HSV1/2 immunoblot(*Herpes Select)*
    - Sensitivity 97-100%, Specificity 96-97%
  - HSV2 IgG ELISA
    - Sensitivity 96-100%, Specificity 94-98%
- Biokit/Fisher Scientific
  - BiokitHSV-2 & SureView (point of care test) (HSV-2 only)
    - Sensitivity 93-96%, Specificity 95-98%
- Trinity Biotech
  - Captia ELISA (HSV-2 only)
    - Sensitivity 90-92%, Specificity 91-98%

Indications for Diagnostic Uses for HSV Serology Tests

- Suspicious lesions that are culture negative
- Suspicious lesions too late or too dry to culture
- Atypical presentations of genital herpes
- Recurrent undiagnosed genital ulcer
- Acquisition > 6 weeks prior

Guerry et al, CID 2005; 40(1): 38-45

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Rationale for HSV-2 Serologic Screening

- Up to 80% of those seropositive for HSV-2 unaware of their infection
- Of these, 75% atypical, 25% asymptomatic
- Patients can be taught to recognize symptoms; treat as needed
- Patients may be motivated to reduce risk behavior and/or protect partners

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Arguments Against HSV Screening

- Unproven benefit
  - May not change clinical management
  - Effect on sexual risk behavior unknown
- Potential significant costs
  - Expensive ($20-60)
  - Potential for adverse psychological impact
  - Increase demand on health care system
  - Potential for unnecessary interventions (i.e. C-section)

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Recommended Use of HSV-2 Serology Tests for Screening

Screening in patients at risk for STD/HIV	**should be offered to select patients**
Screening in HIV-positive patients	**should generally be offered**
Screening in patients in partnerships with HSV-2 infected people	**should generally be offered**
Universal screening in pregnancy	**should generally not be offered**
Screening in general population	**should not be offered**

Guerry et al. CID 2005; 40(1): 38 - 45

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HSV T-S Serology Testing
Limitations

- Does not tell
  - How long infected
  - If person has had or will have symptoms
  - How likely a person is to shed asymptomatically
  - Where infected (HSV-1)
- Cannot diagnose a lesion
- False negatives
  - 77% of patients have antibodies by 6 weeks after HSV-2 primary infection and 59% after HSV-2 non-primary infection.
- False positives
  - Decreased PPV in low prevalence populations AND in patients with HSV-1 infection

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Treatment and Prevention

Overview of Treatment and Prevention of HSV-2

- No cure for HSV-2 nor an effective vaccine
- Condoms effectively decrease transmission—but must be used consistently and correctly, even in absence of symptoms
- Antiviral therapy decreases duration of outbreaks, frequency of symptomatic recurrences, asymptomatic shedding and transmission to uninfected partners
- No intervention shown to decrease risk of neonatal herpes

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Genital Herpes Treatment Modalities

- Treatment of primary episode
- Episodic treatment of recurrent episodes
- Episodic suppression (e.g., special events)
- Long term suppression
  - To reduce outbreaks
  - To reduce transmission

Genital Herpes: CDC Treatment Recommendations

	1st Clinical GH Episode (mg for 7-10 days)	Recurrent Genital Herpes	
		Episodic (mg × days)	Suppressive (mg, daily)
ACV	400 TID	400 TID x 5 d 800 BID x 5 d 800 TID x 2 d	400 BID
FCV	250 TID	125 BID x 5 d 1000 BID x 1 d	250 BID
VCV	1000 BID	500 BID x 3 d 1000 QD x 5 d	500 QD‡ 1000 QD§

FCV=famciclovir; ACV=acyclovir; VCV=valacyclovir.
‡≤9 episodes/yr. §>9 episodes/yr.

Treatment differs for HIV infected patients

Centers for Disease Control and Prevention. *MMWR.* 2006;55(RR-11)1-94.

Episodic versus Suppressive Therapy

- Episodic therapy
  - Decreases healing time by 2 days
  - Decreases pain by 1 day
  - Decreases viral shedding by 2 days
  - Aborts ~25% lesions if taken during prodrome
- Suppressive therapy (short or long term)
  - Decreases frequency/severity of symptomatic recurrences
  - Decreases subclinical viral shedding
  - Decreases transmission

Treatment Goals of Recurrent Herpes

- Improve psychological well-being and reduce psychosocial and psychosexual morbidity
- Enhanced control of disease
- Reduce asymptomatic and symptomatic shedding
- Decrease risk of transmission of HSV virus (suppression only)
  - Person-to-person spread
  - Prevent need for Caesarean section (and maybe neonatal herpes)

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Short-term Suppression

- Suppressive treatment for 1-3-months
- Treatment scenarios
  - Major life events i.e. weddings, final exams, vacations
  - Maximize transmission protection of pregnant partner
  - To evaluate herpes symptoms or differentiate herpes symptoms from other symptoms
- Use suppressive therapy dosage indicated for each antiviral agent
- Treatment must be initiated ~ 5 days in advance of desired event

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Considerations for Suppressive Therapy

- Patient choice and willingness to take medication every day
- Frequent recurrences
- Severe recurrences (independent of frequency)
- Anxiety associated with recurrences
- Concern about preventing a recurrence
- Concern about impact of recurrences on sexual behavior and social circumstances
- Transmission

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Long-term Suppressive Therapy: When to stop?

- Individual assessment
- Frequency of symptomatic outbreaks and psychological adjustment diminish over time
- CDC recommends discussing discontinuing suppressive therapy periodically (1x year)
- No safety concerns (daily acyclovir for > 6 years shown to be safe. No resistance in immune competent patients).

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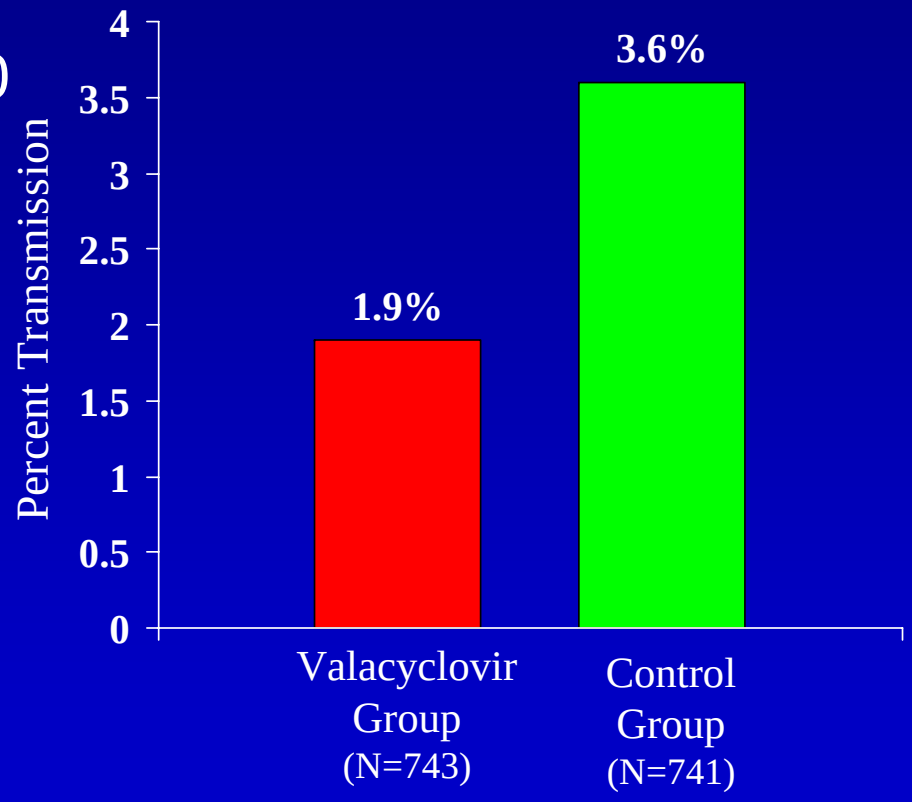
Rates of Transmission of HSV-2 to Susceptible Partners is Reduced with Once-Daily Suppressive Therapy

- 1484 heterosexual couples randomly assigned to take 500 mg of valacyclovir or placebo once daily for 8 months
- Serum samples collected monthly from susceptible partners for HSV analysis
- The valacyclovir group showed
  - decreased transmission
  - lower frequency of shedding
  - fewer copies of HSV-2 DNA when shedding occurred



Corey et al, NEJM 2004; 350(1):11-20.

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Condom Efficacy

- Women with HSV-2 infected partners were protected from acquisition if condoms used >25% of sex acts.

- Men at high risk for STDs were protected from acquisition if condoms used >65% of sex acts.

Wald, JAMA 2001. Wald, Annals, 2005.

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Suppressive Therapy in Pregnancy

Level B (limited/inconsistent evidence)

- Antiviral rx for primary maternal infection
- Consider antiviral rx after 36 weeks in woman with primary infection during this pregnancy

Level C (consensus or expert opinion)

- Antiviral rx after 36 weeks in recurrent GH

ACOG practice guidelines 1999

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Genital Herpes Vaccine Development

- Best strategy to slow epidemic of HSV
- Vaccine trials ongoing since 1920
- **GlaxoSmithKline Herpes Vaccine Efficacy Study Group**
  - Effective only in HSV-naïve women
  - Protects against symptoms of genital herpes, although not against acquisition of HSV-2 virus

HSV: Patient Education

- Nature and chronicity of infection
- Transmission risks: both symptomatic and asymptomatic viral shedding
- Abstinence when lesions or prodrome
- Neonatal transmission risks
- Increased risk of acquisition/transmission of HIV
- Disclosure/protection of partners
- Partner referral for symptoms or serologic testing
- Condoms somewhat protective
- Role of suppression therapy
- Identification of prodrome and use of therapy for recurrence

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Genital Herpes Resources

National Herpes Resource Center ASHA

- http://www.ashastd.org/herpes/herpes_overview.cfm
- Hotline: 1-800-227-8922
- Discussion boards

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